Novel Polyvinylpyrrolidone-Based Lipoplex Modifiers For siRNA Delivery.

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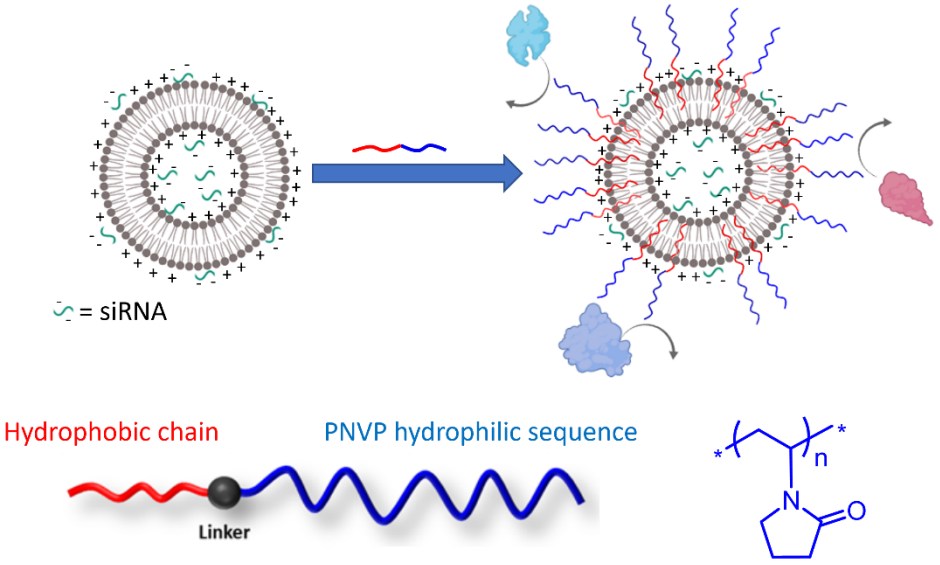
Liposomes are carriers of choice for numerous drug delivery applications.[1] The latter allows to incorporate a wide variety of hydrophilic and lipophilic drugs, to preserve the stability of these compounds and reduce the exposure of the organs to potentially toxic drugs. In particular, siRNA-loaded lipoplexes, resulting from the electrostatic interactions between the polar headgroups of cationic phospholipids and the phosphate groups of siRNA, are promising drug delivery vehicles for cancer therapy.[2] Pegylation of lipoplexes is a common strategy to prevent their rapid elimination by macrophages and prolong their circulation time in blood.[3] Nevertheless, pegylated liposomes/lipoplexes have some limitations as PEG may cause immunological responses as well as Accelerated Blood Clearance (ABC effect), which induces their recognition and elimination from the body.[3] As alternative to PEG, herein, we explore the use of novel poly(*N*-vinylpyrrolidone) (PNVP) derivatives for the modification of siRNA-loaded lipoplexes. A series of well-defined amphiphilic PNVP-based polymers composed of a single or double aliphatic chain were synthesized by Reversible Addition Fragmentation chain Transfer (RAFT). The impact of the nature of the hydrophobic group and of the PNVP molar mass on their insertion within lipid bilayers was studied by quartz crystal microbalance with dissipation monitoring (QCM-D). Dynamic light scattering and zeta potential analyses of the post-modified lipoplexes confirmed the ability of some PNVP derivatives to incorporate within the membrane and to shield the positive charges of the lipoplexes. Additional tests also demonstrated the capacity of these innovative lipoplex modifiers to prevent protein adsorption. In the future, *in vitro* and *in vivo* tests will be performed to further assess the relevance of PNVP as alternative to PEG for the modification of siRNA-lipoplexes.



References:

[1] Allen, T. M. Liposomal Drug Formulations: Rationale for Development and What We Can Expect for the Future. *Drugs* **1998**, *56* (5), 747–756.

[2] Berger, M.; Lechanteur, A.; Evrard, B.; Piel, G. Innovative Lipoplexes Formulations with Enhanced SiRNA Efficacy for Cancer Treatment: Where Are We Now? *Int. J. Pharm.* **2021**, *605* (June).

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